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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: ZICHE=1

In re Application of:) Conf. No.: 5690
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Marina ZICHE et al) Art Unit: 1653
))
Appln. No.: 09/756,185) examiner: R. Mitra
))
Filed: January 9, 2001) Washington, D.C.
))
For: COMPOUND B AS ANGIOGENIC) January 2, 2003
AGENT IN COMBINATION WITH)
HUMAN GROWTH FACTORS)

Response

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, Mail Stop
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

The present communication is responsive to the official action of April 22, 2003. Claims 3, 4, 6 and 10-25 presently appear in this case. No claims have been indicated as being allowable, although it is noted that claims 4, 10, 13, 14, 17, 18, 21 and 22 have not been subject to any rejection. The remaining claims have been rejected. The official action of April 22, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to the use of Compound B combined with human growth factors in promoting angiogenesis. Such a combination can be used as cicatrizers to treat wounds, ulcers and other traumatic lesions. The combination of Compound B and human growth factor has a synergistic effect.

Claims 15, 16, 19 and 23 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that claims 15 and 16 are indefinite because it is not possible for the separate administration dose because Component B and human growth factor are in the same composition. This part of the rejection is respectfully traversed.

Claims 15 and 16 are not dependent from pharmaceutical composition claims, such as claim 3. They are ultimately dependent from method claim 11. Method claim 11 does not require that the Component B and the human growth factor be present in the same composition. It is not understood why the examiner takes this position. Claim 11 only requires that they both be administered. There is no requirement in claim 11 that they be in the same composition. Indeed, the present specification states on page 6, lines 19-22, in discussing the synergistic effect of Component B and bFGF that "... when CB and bFGF were released independently by

2 separate pellets the effect was higher." Accordingly, reconsideration and withdrawal of this part of rejection are respectfully urged.

The examiner states that claims 19 and 23 are indefinite for the term "relative amount" as it is not clear what is that amount that would provide synergistic results and because it is not clear whether Component B is capable of synergizing with a growth factor or vice versa. This part of the rejection is also respectfully traversed.

The term "synergistic angiogenesis results" is clear to one of ordinary skill in the art. This means that the results of the combination of the two components are better than the additive effects of each. For any given composition, it does not matter whether Component B is termed as being synergistic with human growth factor or vice versa. All that matters is that administration of both in the specified relative amounts provides results that are greater than the expected additive effects of each one when administered alone. Therefore, it is not necessary to specify which component is synergizing with the other in order for the claim to be definite. With respect to "relative amounts", the claim is specifying these amounts functionally. It is permissible to use functional definitions of amounts, such as "effective amount", in claims. Those of ordinary skill in the art can

determine which relative amounts provide the required synergistic results and which do not, by routine experimentation. Accordingly, this language is not indefinite. Reconsideration and withdrawal of this part of the rejection is respectfully urged.

Claims 3, 6, 19 and 23-25 have been rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claim 1 of U.S. patent 5,998,364 in view of Folkman. The examiner states that claims 11-25 disclose a method of treatment of wounds, ulcers or other traumatic lesions by administering in a single administrative dose an effective amount of Component B and an effective amount of human growth factor. The examiner considers this to be an obvious variation of claim 1 of the '364 patent, which discloses a method of treatment of wounds, ulcers and other traumatic lesions to any of the tissues of the body by administering an effective amount of Component B together with a pharmaceutically acceptable carrier. The examiner considers that claims 11-25 encompass administering an effective amount of Component B as set forth in claim 1 of U.S. '364 and, therefore, this creates a double patenting situation. The examiner states that any of claims 11-25 in the current application would anticipate claim 1 in the '364 patent. This part of the rejection is respectfully traversed.

This part of the double-patenting rejection appears to be based on the examiner's observation that claim 1 of the '364 patent is broad enough to encompass the process of the presently-claimed invention. However, the examiner's attention is invited to MPEP §804.II, where it states:

Domination and double patenting should not be confused. They are two separate issues. One patent or application "dominates" a second patent or application when the first patent or application has a broad or generic claim which fully encompasses or reads on an invention defined in a narrower or more specific claim in another patent or application. Domination by itself, i.e., in the absence of statutory or non-statutory double patenting grounds, cannot support a double patenting rejection.

All of the present claims require that both Component B and a human growth factor be administered. Claim 1 of the '364 patent does not mention the use of human growth factor. Human growth factor is not "a pharmaceutically acceptable carrier". There is nothing in claim 1 of the '364 patent which would provide any motivation whatsoever to add any human growth factor to the composition used in the method of claim 1. Without motivation to co-administer human growth factor, no *prima facie* case of obviousness has been established by the examiner. As stated in MPEP §804.II.B.1.:

A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent

principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination.

In a 35 U.S.C. §103 rejection, the examiner would never reject a claim for the administration of A and B based on a reference that only discloses the administration of A. Thus, the same is impermissible in a double patenting analysis. Accordingly, reconsideration and withdrawal of this part of the rejection are respectfully urged.

The examiner further states that Folkman teaches several angiogenic proteins, e.g., bFGF and vEGF, whose angiogenic activity can be synergistic with one another. The examiner states that Folkman does not teach a composition that comprises Component B, but that claims 3, 6, 19 and 23-25 of the present application and claim 1 of the '364 are obvious variations of a method of treatment of wounds, ulcers and other traumatic lesions by administering the combination of Component B and hGF. The examiner states that the '364 patent claim in combination with Folkman teaches the combined composition of the currently claimed method. This rejection is respectfully traversed.

First of all, with respect to claim 11, which is directed to a method of promoting angiogenesis, there is nothing in claim 1 of the '364 patent that would teach or disclose this utility. The '364 patent does not teach or suggest that Component B can be used as an angiogenic agent, nor does it teach or suggest use of Component B together with human growth factors for causing angiogenesis. While Folkman teaches that two human growth factors can act synergistically with one another, this would in no way teach or suggest that Component B has angiogenic activity, nor would it teach or suggest that a human growth factor can act synergistically with Component B.

With respect to claim 20, and those claims dependent therefrom, the '364 patent mentions the use of Component B as anti-inflammatory, anticoagulant, antitumorigenic, and cicatrizing for the treatment of wounds, ulcers and other traumatic lesions of the body. There is no teaching or suggestion that Component B has angiogenic properties. Folkman teaches that two growth factors have synergistic angiogenic effects when combined with one another, as compared to the use of each alone. As the references teach different effects, it would not be obvious to combine them.

Furthermore, any *prima facie* case of obviousness for combining the two reference would be overcome by the proof of

unexpected results shown in the present specification.

Reference is made to Figures 4A and 4B of the present application. In Figure 4A it can be seen that the angiogenic score over time for 500 ng of Component B (CB) alone and for 100 ng basic fibroblast growth factor (bFGF) alone can be seen. In Figure 4B, one can see the angiogenic score for 500 ng of CB administered with 100 ng bFGF. The angiogenic score when the two compounds are administered together (e.g., 4.8 on day 7) is clearly more than the sum of the angiogenic scores when the two compounds were administered separately (1 for bFGF and 1.2 for CB on day 7; sum equals 2.2).

In Table 3, the synergistic effect between Component B and vascular endothelial growth factor (vEGF) can be seen. When 500 ng CB is used alone, one out of five implants was scored as positive. When 100 ng of vEGF was used alone, one out of four implants was scored as positive. In contrast, when 400 ng of CB was used in conjunction with 100 ng of vEGF, four out of four implants were scored as positive. Clearly the two compounds work synergistically, in that the effect of the two together is greater than the sum of their separate effects.

Accordingly, even if the examiner has established a *prima facie* case of obviousness (and it is not believed that the examiner has done this for the reasons discussed above),

this *prima facie* case of obviousness has been rebutted by the showing of synergistic results presented in the present specification. The examiner states that Folkman teaches that synergism would be expected. However, Folkman only teaches that when bFGF and vEGF are used together they provide synergistic results as compared to the use of either one separately. There is no suggestion that the use of either of these will provide synergistic angiogenic effects if combined with Compound B, particularly since there is no prior art that discloses that Compound B has angiogenic effects at all. Reconsideration and withdrawal of this double patenting rejection are, therefore, respectfully urged.

Claims 3, 6, 11, 12, 19, 20 and 23-25 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martelli taken with Folkman. The examiner states that Martelli discloses a pharmaceutical composition comprising Component B as active ingredient, together with a pharmaceutically acceptable carrier for the treatment of wounds, ulcers and other traumatic lesions. The examiner states that Folkman teaches several angiogenic proteins whose angiogenic activity can be synergistic. The examiner concludes that in view of the fact that Martelli teaches Component B in a composition, it would have been obvious to one of skill in the art to have combined Martelli's Component

B with Folkman's angiogenic protein to give synergistic results. This rejection is respectfully traversed.

Martelli is the PCT equivalent of the '364 patent relied upon by the examiner in the double patenting rejection.

Accordingly, their disclosures are identical. The issues in this 35 U.S.C. §103 rejection are identical to the issues in the double patenting rejection discussed above insofar as it relates to the combination of the teachings of Martelli with Folkman. Accordingly, the reasons given hereinabove why the present claims are not obvious from any disclosure of the '364 patent with Folkman are equally applicable to the rejection based on the corresponding PCT application with Folkman. Reconsideration and withdrawal of this rejection for the same reasons as discussed above with respect to the double patenting rejection are, therefore, respectfully urged.

As pointed out above, claims 4, 10,13, 14, 17, 18, 21 and 22 have not been subjected to any rejection. Accordingly, it is respectfully requested that the examiner confirm that these claims would be allowable if rewritten in independent form.

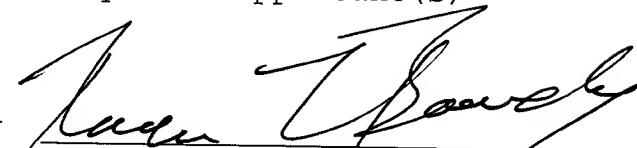
It is submitted that all of the claims now present in the case clearly define over the references of references of record and fully comply with 35 U.S.C. §112.

Reconsideration and allowance are, therefore, earnestly
solicited.

Respectfully submitted,

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